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Screening People with Persistent Absolute Lymphocytosis Favors the Identification of High-Count Monoclonal B-Cell Lymphocytosis.

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OBJECTIVES

- Determine the prevalence of monoclonal B-cell lymphocytosis (MBL) in a cohort of individuals with persistent absolute lymphocytosis (PAL).
- Characterize the subtypes (CLL-like, atypical, non-CLL-like) of MBL found within the PAL cohort.
- Compare the ratio of high-count MBL (hcMBL) to low-count MBL (lcMBL) in the PAL cohort with that found in the general population.
- Analyze differences in age, immunoglobulin light chain restriction, and immune microenvironmental parameters in hcMBL and lcMBL patients.

CONCLUSIONS

- The PAL cohort exhibited a higher proportion of hcMBL (64%) than typically observed in the general population (5%), suggesting that PAL is a strong indicator for the presence of this pre-leukemic condition.
- hcMBL and lcMBL demonstrate distinct characteristics, including differences in age, immunoglobulin light chain usage, and immune cell profiles (T-cells and monocytes).
- The altered immune microenvironment in hcMBL, characterized by lower T-cell counts and higher monocyte counts, may reflect an ongoing immune response to the clonal B-cell expansion or represent an inherent characteristic of this subgroup, potentially influencing progression to CLL.
- Screening for MBL in individuals with PAL is a valuable strategy to identify a cohort of people with hcMBL that can be followed to study the natural history of MBL and understand the factors that contribute to its transformation into CLL. This might pave the way for potential early intervention strategies to prevent conversion to CLL.

Feinstein Institutes for Medical Research
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INTRODUCTION

Monoclonal B-cell lymphocytosis (MBL) appears to be an obligate precursor state for the development of CLL. Moreover, MBL is associated with a higher likelihood of developing other types of cancers and of experiencing severe infection. MBL is a common finding in the aging population, with a reported average prevalence of 15% in individuals between 40 to 100 years. MBL is divided to 2 categories, lcMBL (< 500 cells/ul), which represent ~95% of cases, and hcMBL (500-4,999 cells/ul), representing ~ 5% of cases. Since people with hcMBL progress to CLL at rate of ~1-5% per year, identifying those people with hcMBL who will progress to CLL is a unrealized goal. Were this achievable with sufficient accuracy, this might allow pre-emptive, preventive therapy. Random population-based studies have provided valuable information about MBL prevalence. Additionally, developing a screening approach that would favor identifying people with hcMBL who could be followed prospectively to define the natural history and understanding the pathobiology that predisposes to CLL, other cancers, and severe infections. Here we show that focusing on individuals with persistent absolute lymphocytosis (PAL) offers a targeted strategy for identifying hcMBL, thereby allowing studies to improving our understanding of this pre-leukemic condition.

METHODS

This study investigated the prevalence and characteristics of MBL within a well-defined cohort of patients with PAL. We define PAL as an absolute lymphocyte count (ALC) above 3.3 x 10^9/L that lasts for at least 90 days and is not interrupted by a normal ALC. All participants found to have PAL underwent multiparameter flow cytometry analysis using a comprehensive panel of antibodies targeting B-, T-, and myeloid-cell markers.

RESULTS

- Of the 608 PAL patients screened, 14% (85) had a clonal B-cell expansion, indicative of MBL. Detailed flow cytometry analyses of 71 MBL cases defined the distribution of MBL subtypes: 66% (47) CLL-like MBL ($CD5^+CD20^{Dim}$), 5.4% (4) atypical MBL ($CD5^+CD20^+$), and 20.3% (15) non-CLL-like MBL ($CD5^-CD20^+$). These frequencies are consistent with those previously reported. Seven percent (5) of the clonal B-cell expansions did not fall into any of these categories. Although the prevalence of CLL-like MBL aligns with that reported in the general population ≥ 40 years old, the ratio of hcMBL to lcMBL is strikingly different, i.e., 64% vs 36% in our series compared to 5% vs 95% in reported random analysis ($P < 0.0001$). This highlights the effectiveness of the PAL approach for enriching the identification of clinically relevant hcMBL cases.
- The median age for the PAL cohort excluding the MBL cases was 60.6 years (range 38-100), while the median age for the MBL group was 70.3 years (range 38-97; $P < 0.0001$). Within the MBL group, the median age for hcMBL cases was 71 years (range 55-97), and for lcMBL cases was 66.5 years (range 49-87) (not significantly different).
- Immunoglobulin (IG) light (L) chain analysis revealed a predominance of Igκ L chains in lcMBL clones (14 κ, 3 λ) and a Igλ L chain clonal bias in hcMBL (11 κ, 17 λ, and 2 with no detectable L chain restriction).
- Analysis of the cellular immune microenvironment revealed significant differences between healthy controls (HC), PAL individuals without clonal expansions, and the MBL subgroups. All PAL exhibited significantly higher absolute T-cell counts compared to HC. However, people with hcMBL had significantly lower T-cell counts than both PAL and lcMBL patients ($P < 0.05$). This pattern was mirrored in the $CD4^+$ T-cells, while $CD8^+$ T cells showed no significant differences with the MBL cases and HC. Interestingly, monocyte counts were significantly higher in MBL cases compared to HC, with a more pronounced elevation observed in the hcMBL subgroup.

Table. Characterize of PAL subjects

PAL (72)	No clonal expansion	CLL like MBL		Atypical MBL	nonCLL-like
		lcMBL	hcMBL		
number of subjects	8	14	31	4	15
Age	21-74	49-87	57-95	46-85	68-85
Gender M/F	3/5	3/11	18/12	3/1	8/7
Igκ major clone		12	11		
Igλ major clone		2	17		
Igκ/Igλ neg clone			2		

Fig 1. High incidence of hcMBL in Male

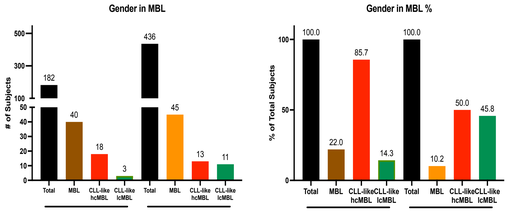


Fig 2. hcMBL patients had significantly lower T-cell counts than both PAL and lcMBL patients

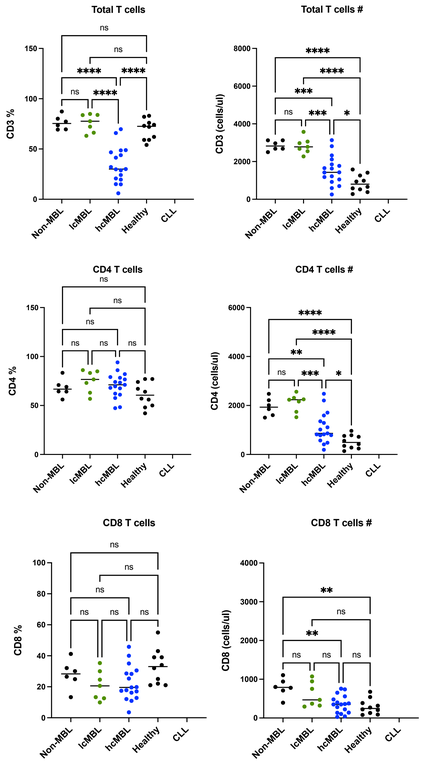


Fig 3. MBL patients had significant higher monocytes compare to heathy control

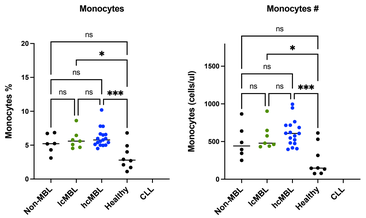
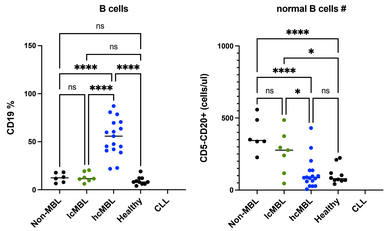


Fig 4. PAL patient had significant high polyclonal B cells compare to hcMBL and healthy control



DISCLOSURES

No